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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/393,803	09/10/1999	MARGARET A. LIU	19188PCA	3309

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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/393,803	Applicant(s) LIU ET AL.	
	Examiner Gerald Leffers	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-22,25,39-41 and 44-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,5-18,21,22,39,41,44,45,48,49* is/are allowed.

6)☐ Claim(s) *19,20,25,35,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 4/18/02 as Paper No. 13, in which claims were cancelled (claims 2-4 and 42), claims were amended (claims 1, 5, 12, 19-20, 25, 35, 44-45) and new claims were added (claims 46-49). Claims 1, 5-22, 25, 35, 39-41, 44-49 are pending in this application.

Any rejection of record in previous office actions that is not addressed in this action has been withdrawn. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a new rejection necessitated by applicants' amendment, filed 4/18/02 as Paper No. 13.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Each of the claims is directed towards polynucleotides intended for use in a gene therapy approach for generating an immune response (e.g. a general protective response, neutralizing antibodies or HIV-specific T cell response) against HIV in a vertebrate animal (e.g. humans). The only disclosed use for the claim polynucleotides is for producing a therapeutic or protective immune response in an animal against HIV infection. The nucleic acids of the inventions comprise up to several cistrons per nucleic acid construct which cistrons are either under the control of individual promoter/regulatory elements or feature two or more cistrons operatively linked to a first promoter/regulatory element (e.g. via an IRES sequence located between different cistrons such that a single transcript produces multiple polypeptides upon translation in the cell). The invention thus encompasses the complex expression of multiple coding sequences from single nucleic construct in eukaryotic cells. Moreover, the invention encompasses the use of coordinated expression of gene products and interaction between expressed gene products and the nucleic acid construct itself to affect the ultimate expression of the desired antigenic HIV polypeptide in vivo (e.g. expression of rev from the same construct comprising a rev-dependent gene). Finally, the invention encompasses the additional expression of immuno-stimulatory gene products from the same construct in order to enhance the level and type of immune response against the desired polypeptide. Thus, the claimed invention is exceedingly complex on multiple levels from transgene expression in eukaryotic cells to coordinate expression of gene products to stimulation of the immune response of a vertebrate organism via the expression of "foreign" genes in vivo.

Breadth of the claims: Given the broadest reasonable interpretation of the rejected claims upon reading the specification, the claims read upon the vaccination of a vertebrate animal,

specifically humans, against infection by HIV. Thus, the breadth of the rejected claims, encompassing a vaccine against a pathogen for which no effective vaccine is known even at this time, only exacerbates the extreme complexity of the claimed invention.

Guidance of the specification: The specification provides many permutations of different nucleic acid constructs bearing multiple cistrons that can be tried in an effort to develop a safe and effective HIV vaccine. Guidance is given for different types of constructs wherein the different cistrons are each transcribed under the control of separate regulatory elements or wherein the different cistrons on a given construct are transcribed as part of a single, polycistronic message. Different combinations of immunostimulatory and antigenic coding sequences are described which might be tried in order to develop an effective immune response against a pathogenic organism from which the antigen coding sequence is derived. There is no significant guidance, however, with regard to making the construction and use of such an anti-HIV vaccine in humans more predictable than had already been demonstrated in the art at the time of applicants' filing of the instant application.

The existence of working examples: Although applicants test various polynucleotide constructions in mice and primates, these systems are not acknowledged models that would reflect the human conditions (e.g. see Haynes below). The specification provides examples wherein nucleic acid constructs of the invention were used to generate an anti-gp120 response in mice, anti-gp160 response in primates (i.e. the rhesus monkey and African green monkey) and an anti-SIV response in primates. The anti-gp120 response in mice demonstrated that the polycistronic vectors described as part of the instant invention are more effective than the equivalent combination of monocistronic vectors in generating a specific immune response

against gp120. However, as noted above, none of the model systems described by applicants is accepted in the art as being predictive of success for developing such an anti-HIV vaccine or protective response in humans. Moreover, applicants own examples demonstrate that the generation of a sustained, specific immune response in lower primates is not necessarily predictable with the nucleic acid constructs of the instant invention. In the case of an anti-SIV response, applicants' construct generated a specific CTL response against SIV gag that is subdued over time. No such specific CTL response was obtained for equivalent constructs expressing SIV nef (e.g. Example 4).

State of the art: The art of vaccinating vertebrate organisms against viral infections, at the time of filing of the instant application, was well developed. However, the unique challenges presented by the HIV virus, due to its nature of attacking the helper T cell subset, present heretofore insurmountable challenges. "The difficult scientific issues before us underlie the fact that, as yet, there is no preventive HIV vaccine on the near horizon with clear prospects for clinical use." (Haynes, page 1279, column 1). "Although more is known about HIV than almost any other infectious agent, scientific questions remain unanswered that are critical to development of an HIV preventative vaccine." (Haynes, page 1279, column 3). Further, there are no animal models for human infection. "Because of a lack of an animal model of human AIDS and because a cohort of individuals naturally resistant to HIV infection is not available, the immune correlates of protection against HIV are not known." (page 1280, column 1). Thus, the state of the art with regard to an immune response by humans against HIV, remains underdeveloped and extensive experimentation of a discovery nature is ongoing.

Predictability of the art: The art of vaccinating a vertebrate host organism against HIV viral infection or viral epitopes is unpredictable. At the time of applicants' invention, there was no model organism that exhibited an immune response to HIV that was correlative with that of humans. It is also known in the art that the surface antigens of the virus mutate rapidly, thus evading immune responses and that no protective immunity has been raised against HIV, even to date. Thus, the art of vaccinating a vertebrate against HIV infection is unpredictable.

The amount of experimentation necessary: Given the extreme complexity of the invention, featuring the use of nucleic acids directly injected into the tissue of an organism that must coordinately express multiple genes in vivo and that must generate an immune response against at least one of the gene products; given the fact that the breadth of the claims encompasses a vaccine against a pathogen for which no such effective vaccine has been developed; given the lack of significant guidance in the specification on how to make and use such nucleic acid constructs to generate such an in vivo immune response against HIV; given the lack of relevant working examples and the fact applicants' own examples with primates are not predictable (much less predictable of success in humans); given the state of the art at the time of the invention where no such vaccine against HIV was known nor was thought to be available any time in the near future; and given the resulting unpredictability of the art that arises from the fact that no such vaccine has been developed to date, and the fact that HIV attacks the very cell population responsible for specific anti-viral response and the nature of the highly mutable HIV virion, one of skill in the art would not be able to construct and use the claimed invention without undue, unpredictable experimentation. Thus, applicants' invention of polycistronic

nucleic acid constructs and methods for inducing a protective immune response against HIV in vertebrate animals, including humans, is not considered enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-20, 25 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **The following rejections were necessitated by applicants' amendment of the claims in Paper No. 13.**

Claim 19 is vague and indefinite in that it appears to specify that an antigenic epitope is selected from a series of different nucleic acid sequences. While nucleic acids can be antigens, it appears from reading the specification that the claim is more probably directed towards an epitope obtained from a protein encoded by each of the recited coding sequences.

Claim 20 is vague and indefinite in that it appears to specify that an immunogenic epitope is selected from a group of different proteins. Entire proteins are not normally referred to as an epitope. It appears from reading the specification that the claim is more likely directed towards an immunogenic epitope obtained from one of the recited proteins rather than comprising the entire protein.

Claim 25 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the mammal" in claim 1, upon which claim 25 is dependent.

Claim 35, step f, is vague and indefinite in that step f recites the limitation of "a transcription-termination signal 3' of the most downstream open reading frame of step d) or

optionally, step f)". It is unclear what is intended when the step refers back on itself. It would be remedial to amend the claim language to clearly indicate what other step (e.g. step e?) is meant to be referred to by the limitation of step f.

Conclusion

Claims 19-20, 25, 35 and 46-47 are rejected. Claims 1, 5-18, 21-22, 39-41, 44-45 and 48-49 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

ggl
June 27, 2002

DAVID GUZO
PRIMARY EXAMINER